尖端赛多孢子菌肺部感染的临床特征及预后分析

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【摘要】 目的 分析尖端赛多孢子菌引起的肺部感染的临床特征、治疗及预后,为临床诊断和治疗提供依据。**方法** 收集2018年1月—2021年12月在复旦大学附属中山医院感染病科治疗的尖端赛多孢子菌肺部感染的患者共8例,回顾性分析患者的临床特征、影像学表现、治疗及预后。**结果** 8例患者中,男性3例,女性5例,平均年龄58(27~76)岁。经MALDI-TOF MS鉴定,6例为尖端赛多孢子菌,2例为波氏假阿利什菌。8例患者中1例无基础疾病;1例有系统性硬化症合并肺间质病变、糖尿病,长期服用强的松10 mg/qd、赛可平0.5 g/qd;其余6例伴有肺部基础疾病。最常见的临床症状为咳嗽,其余依次为咳痰、痰血/咯血、发热、气急、消瘦。患者的平均BMI为19.5(15.6~23.2) kg/m^2,4例患者BMI<18.5 kg/m^2。实验室检查方面,所有患者的白细胞计数、中性粒细胞计数、降钙素原均正常;红细胞沉降率(erythrocyte sedimentation rate,ESR)平均为32 mm/h(4例升高);高敏C反应蛋白(high sensitivity C-reactive protein,hs-CRP)平均为24.8 mg/L(5例升高)。G试验和GM试验阴性。患者的CD4淋巴细胞计数平均为512.8(226.0~943.0)/μL,5例CD4淋巴细胞计数<500/μL。患者的胸部CT表现多样:支气管扩张(5例)、结节(3例)、实变(3例)、空洞(2例)、胸膜增厚(2例)、树芽征(2例),各种影像学表现往往合并存在。所有患者均首选伏立康唑治疗,4例患者服药后出现肝功能不全、幻视予停药或调整为泊沙康唑治疗。随访至治疗开始后6个月,所有患者的临床症状均明显好转;影像学上,5例病灶好转吸收,2例病灶相仿,1例病灶增多,考虑为合并胞内分枝杆菌感染所致。**结论** 尖端赛多孢子菌肺部感染的临床症状和影像学表现缺乏特异性,仅炎症标志物ESR和hs-CRP轻度升高,G试验和GM试验阳性率低,因此早期诊断困难。治疗首选伏立康唑,患者总体预后良好。

【关键词】 尖端赛多孢子菌; 肺部感染; 临床特征; 预后
【中图分类号】 R563.1,R44 **【文献标志码】** A **doi**:10.3969/j.issn.1672-8467.2023.05.002

Clinical manifestations and outcomes of pulmonary infection by *Scedosporium apiospermum*

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【Abstract】 Objective To summarize the clinical characteristics and outcomes of localized pulmonary infection by *Scedosporium apiospermum* (*S. apiospermum*) in order to provide evidence for diagnosis and treatment. **Methods** We reviewed 8 patients diagnosed with *S. apiospermum* pulmonary infection from Jan 2018 to Dec 2021 at the department of infectious disease of Zhongshan Hospital, Fudan University. The clinical data, radiological findings, treatment and prognosis of the patients were analyzed retrospectively. **Results** Among the 8 patients, there were 3 males and 5 females, with an average age of 58 (27–76) years. Identified by MALDI-TOF MS, 6 cases were *S. apiospermum* and 2 cases were *S.*

国家重点研发计划(2021YFC2300400);上海申康医院发展中心重大临床研究项目(SHDC2020CR2031B);复旦大学附属中山医院科研发展基金(2021ZSFZ17)
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网络首发时间:2023-09-15 14:21:52 网络首发地址:https://link.cnki.net/urlid/31.1885.R.20230914.1442.002

boydii. There was 1 case had systemic sclerosis with pulmonary interstitial disease and diabetes, treated with Prednisone 10 mg/qd and Mycophenolate Mofetil 0.5 g/qd, 6 cases were accompanied by underlying pulmonary diseases, and 1 case had no underlying disease. The most common clinical symptoms were cough, followed by sputum production, haemoptysis, fever, dyspnea and weight loss. The mean BMI was 19.5 (15.6-23.2) kg/m^2, and the BMI was less than 18.5 kg/m^2 in 4 cases. The white blood cell counts, neutrophil counts and procalcitonin (PCT) were normal in all patients. The average value of erythrocyte sedimentation rate (ESR) and high sensitivity C-reactive protein (hs-CRP) were 32 mm/h (increased in 4 cases) and 24.8 mg/L (increased in 5 cases). G test and GM test were negative. The average CD4 lymphocyte count of patients was 512.8 (226.0-943.0) /μL, and the counts of 5 cases were <500/μL. The chest CT findings were diverse: bronchiectasis (5 cases), nodules (3 cases), consolidation (3 cases), cavities (2 cases), pleural thickening (2 cases), and tree bud sign (2 cases), and various imaging findings often existed in combination. All the patients were treated with voriconazole, and 4 patients developed liver insufficient and visual hallucination after taking the medicine were stopped or adjusted to posaconazole. Follow up for 6 months after the start of treatment, the clinical symptoms of all patients were significantly improved. In imaging, 5 cases were absorbed, 2 cases were similar, and 1 case was deteriorated, which was considered to be caused by mycobacterium infection. **Conclusion** The clinical and imaging manifestations of localized pulmonary infection by *S. apiospermum* are non-specific, inflammation markers ESR and hs-CRP are only slightly elevated, and the positive rates of G test and GM test are low, which make early diagnosis difficult. All the patients were treated with voriconazole and the overall prognosis is good.

【Key words】 *Scedosporium apiospermum*; pulmonary infection; clinical manifestation; prognosis

*** This work was supported by the National Key R&D Program of China (2021YFC2300400), the Major Clinical Research Project of Shanghai Hospital Development Center (SHDC2020CR2031B) and the Scientific Research Development Fund of Zhongshan Hospital, Fudan University (2021ZSFZ17).**

赛多孢霉属由一组丝状真菌组成,广泛存在于土壤、污水等自然环境中。随着分子生物学的发展,赛多孢霉属分为尖端赛多孢子菌复合体(*Scedosporium apiospermum* species complex)和多育赛多孢子菌,前者包括至少10个不同物种,其中5个种可引起人类感染:尖端赛多孢子菌、波氏假阿利什菌、微孢假阿利什菌、橙黄赛多孢子菌和德氏赛多孢子菌,一般认为波氏假阿利什菌是尖端赛多孢子菌的有性形式[1-3]。作为机会性感染病原体,尖端赛多孢子菌引起的感染在很大程度上与宿主的免疫状态有关:在免疫功能缺陷特别是实体器官移植、造血干细胞移植患者中,尖端赛多孢子菌可引起危及生命的播散性感染[4];而在免疫功能正常的宿主中多表现为局部感染,如皮肤、关节、呼吸道、心瓣膜等,往往与局部创伤、操作、溺水等有关[2-3]。尖端赛多孢子菌引起的肺部感染临床表现无特异性,常表现为咳嗽、咳痰、咯血、发热、呼吸困难等[5];且尖端赛多孢子菌培养阳性率低、培养时间长,给临床诊断带来很大困难,易漏诊和误诊。

目前有关局限性尖端赛多孢子菌肺部感染的报道多为个案报告或文献综述,且多与溺水相关。我们回顾性分析8例与溺水无关的局限性尖端赛多孢子菌肺部感染病例,探讨其临床特征、治疗及预后,以期为临床诊治提供参考。

资料和方法

研究对象 选取2018年1月—2021年12月在复旦大学附属中山医院感染病科治疗的局限性尖端赛多孢子菌肺部感染患者的临床资料,对其相关资料进行统计分析。

尖端赛多孢子菌肺部感染确诊标准 参考《欧洲癌症研究与治疗组织和真菌病研究组教育与研究联盟(EORTC/MSGERC)对侵袭性真菌病定义的修订和更新》[6],需同时满足如下标准:(1)胸部CT检查证实肺部新发病灶;(2)原有呼吸道症状加

重或新出现呼吸道症状；(3)具备尖端赛多孢子菌感染的微生物学证据(呼吸道标本如痰液、支气管肺泡灌洗液、肺组织真菌培养尖端赛多孢子菌阳性)；(4)无其他可以解释肺部疾病的微生物学依据。排除标准：(1)考虑定植，未予抗真菌治疗；(2)随访未满6个月。最终纳入8例患者。

观察指标　分析患者年龄、性别、基础疾病、临床表现、实验室检查、影像学表现、治疗及转归。实验室检查包括血常规、高敏C反应蛋白(high sensitivity C-reactive protein，hs-CRP)、红细胞沉降率(erythrocyte sedimentation rate，ESR)、降钙素原(procalcitonin，PCT)、白蛋白(Alb)、G试验等。本研究为回顾性分析，豁免知情同意书。

实验室培养技术　将呼吸道标本接种到沙氏葡萄糖琼脂培养基(SDA)，分别在30 ℃和37 ℃下孵育2周。通过观察宏观和微观形态及MALDI-TOF MS对菌落进行菌种鉴定。

结　　果

患者基本临床信息　8例患者中，男性3例，女性5例，平均年龄58(27～76)岁(表1)。培养阳性菌株经MALDI-TOF MS鉴定，6例为尖端赛多孢子菌、2例为波氏假阿利什菌。1例患者有系统性硬化症合并肺间质病变、糖尿病，长期服用强的松10 mg/qd和赛可平0.5g/qd治疗。其余7例患者均无严重的免疫缺陷：1例无基础疾病；2例有哮喘史且长期吸入信必可治疗(1例有肺恶性肿瘤手术史、无放化疗史)；1例有慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)；3例有支气管扩张症(2例有肺结核史，1例有COPD史)。所有患者均无吸烟史。

患者的临床症状无特异性，1例患者无症状，体检行胸部影像学检查时发现病变。6例患者咳嗽，5例脓痰，2例痰血/咯血，2例发热，1例胸闷气急，1例消瘦。患者平均BMI为19.5(15.6～23.2) kg/m^2，其中4例患者BMI＜18.5 kg/m^2。

实验室检查　患者的平均白细胞为6.4(4.2～7.8)×10^9/L、中性粒细胞计数为4.7(3.6～6.1)×10^9/L、中性粒细胞百分比为67.9%(56.7%～78.1%)、CD4淋巴细胞计数为512.8(226.0～943.0)/μL、红细胞沉降率为32(2～70)mm/h、高敏C-反应蛋白为24.8(0.3～88.0)mg/L、降钙素原为0.06(0.02～0.19)ng/mL、白蛋白为42.6(38.0～50.0)g/L、前白蛋白为198.5(119.0～280.0)mg/L。所有患者的白细胞计数、中性粒细胞计数均正常，2例中性粒细胞百分比升高；有5例患者的CD4淋巴细胞计数＜500/μL，但均＞200/μL；4例ESR升高；5例hs-CRP升高；PCT均正常；患者的白蛋白均正常，但5例患者的前白蛋白水平降低。患者的G试验结果平均为28.8(10.0～87.0) pg/mL，均为阴性；5例患者送检血GM试验，均为阴性。

影像学表现　患者的胸部CT表现多种多样，3例为结节样病灶，2例为树芽征，2例出现空洞样病灶，3例出现实变，5例有支气管扩张，2例有胸膜增厚；所有患者均无胸腔积液。影像学表现往往合并存在。

治疗及预后情况　所有患者从出现症状到开始治疗间隔时间平均为377(6～1 831)天。所有患者首选治疗药物均为伏立康唑，疗程3～15个月。1例患者因无明显的临床症状，肺部病灶较轻，治疗3个月后肺部病灶无明显变化，予以停药，密切随访；1例患者服用伏立康唑治疗后出现肝功能不全，同时肺部病灶基本吸收，治疗4个月后停药；1例患者服用伏立康唑后出现幻视，治疗4个月后停药；2例患者在治疗过程中出现肝功能不全，调整为泊沙康唑治疗，疗程均为5个月；其余3例患者疗程分别为5、6和15个月。

随访至治疗开始后6个月，所有患者的临床症状均明显好转。影像学上，2例前后相仿，5例病灶好转吸收，1例病灶增多。病灶增多的患者在抗真菌治疗过程中痰分枝杆菌培养阳性，菌种鉴定为胞内分枝杆菌，考虑合并非结核分枝杆菌感染，同时加用抗分枝杆菌治疗。

讨　　论

随着各种原因引起的免疫缺陷患者的数量逐渐增多，尖端赛多孢子菌感染的发病率也逐渐增高，但仍属罕见。目前有关尖端赛多孢子菌引起的肺部感染多为个案报告或文献综述，且绝大多数病例为溺水后病例或器官移植、血液系统肿瘤化疗后等严重免疫缺陷的患者。本研究首次分析了在免疫功能正常及轻度受损的患者中，尖端赛多孢子菌

表1 尖端赛多孢子菌肺部感染患者的临床特征

Tab 1 Clinical characteristics of the pulmonary scedosporiosis cases

Characteristics	Reference	Patients [n(%)]	Median (range)
Male/female	–	3 (60.0)	
Age (y)	–	–	58 (27-76)
Underlying disease	–	7 (87.5)	
BMI (kg/m^2)	≥18.5	4 (50.0)	19.5 (15.6-23.2)
Symptoms		7 (87.5)	
Cough	–	6 (75.0)	
Sputum production	–	5 (62.5)	
Haemoptysis	–	2 (25.0)	
Fever	–	2 (25.0)	
Dyspnea	–	1 (12.5)	
Weight loss	–	1 (12.5)	
Laboratory testing			
Elevated WBC (×10^9/L)	3.5-9.5	0	6.4 (4.2-7.8)
Elevated neutrophils (×10^9/L)	1.8-6.3	0	4.7 (3.6-6.1)
Elevated percentage of neutrophils (%)	45-75	2 (25.0)	67.9 (56.7-78.1)
Decreased CD4 cell count (/μL)	≥500	5 (62.5)	512.8 (226.0-943.0)
Elevated ESR (mm/h)	Male: 0-34; Female: 0-28	4 (50.0)	32 (2-70)
Elevated CRP (mg/L)	0-3.0	5 (62.5)	24.8 (0.3-88.0)
Elevated PCT (ng/mL)	0-0.5	0	0.06 (0.02-0.19)
Decreased albumin (g/L)	35-55	0	2.6 (38.0-50.0)
Decreased prealbumin (mg/L)	180-350	5 (62.5)	198 (119-280)
G test (pg/mL)	(-)<100.5	0	28.8 (10.0-87.0)
GM test	(-)<0.5	0	0.27 (0.09-0.54)
Imaging findings			
Bronchiectasis	–	5 (62.5)	
Nodules	–	3 (37.5)	
Consolidation	–	3 (37.5)	
Cavity	–	2 (25.0)	
Pleural thickening	–	2 (25.0)	
Tree-in-bud	–	2 (25.0)	

引起局限性肺部感染的相关临床表现及预后,为临床提供参考。

在免疫功能正常的患者中,尖端赛多孢子菌肺炎通常发生在有潜在基础肺部疾病(如支气管扩张、陈旧性肺结核、肺结节病等)的患者中[7]。临床表现多样,可以从无症状到咳嗽、咳痰、咯血、胸痛、盗汗、呼吸困难,常伴有发热、消瘦、乏力等全身症状[8]。本研究中7例(87.5%)患者均有不同程度的全身性或肺部疾病。最常见的临床表现是咳嗽,其次依次为脓痰、痰血/咯血、发热、体重下降、胸闷。这些临床表现较为隐匿,均可由基础肺部疾病引起,对于尖端赛多孢子菌肺炎的诊断缺乏特异性。

影像学上,尖端赛多孢子菌肺炎可表现为实变、渗出、结节、空洞、胸膜增厚、胸腔积液,可出现"树芽征""晕轮征""新月征",与肺曲霉感染很难鉴别[8-11]。本研究中患者的胸部CT表现多种多样,结节、空洞、实变、树芽征、支气管扩张、胸膜增厚等多种影像学表现往往合并存在,与既往个案报告相一致。值得注意的是,这些影像学表现也可见于基础肺部疾病,如支气管扩张、陈旧性肺结核、肺结节病等,缺乏特异性。由于尖端赛多孢子菌肺炎的临床和影像学表现均缺乏特异性,早期诊断和精准治疗难度较大。

在体外,尖端赛多孢子菌对绝大多数抗真菌药

物不敏感或耐药，给治疗带来很大的困难[1]。目前指南推荐治疗首选伏立康唑，必要时可联合使用2种甚至3种抗真菌药物，治疗过程中需密切监测药物不良反应[2,12]。对于疗程目前尚无确切规定[12]，感染的部位和严重程度不同，患者的预后有所不同[7]。既往研究表明，尖端赛多孢子菌引起的局限性肺部感染，死亡率较低[4]。本研究中，所有患者均首选伏立康唑治疗，患者总体预后良好，但有4例（50%）患者在治疗过程中出现肝功能不全、幻视等不良反应，其中2例更换为泊沙康唑继续治疗。

近期有文献报道尖端赛多孢子菌与非结核分枝杆菌合并感染[13]。本研究中，有1例患者在抗真菌治疗过程中肺部病灶持续增多，同时痰分枝杆菌培养阳性，菌种鉴定为胞内分枝杆菌，考虑存在合并感染。随着全世界范围内非结核分枝杆菌感染的发病率不断增加，同时感染尖端赛多孢子菌和非结核分枝杆菌的病例可能也会增加。

目前对于尖端赛多孢子菌感染的诊断主要依赖直接显微镜检、组织病理学及常规的培养方法，而常规培养耗时长、敏感性极低，给诊断带来很大困难。本研究中患者呼吸道标本培养均为阳性，诊断尖端赛多孢子菌感染的平均时间为377（6～1 831）天，远长于溺水病例和播散性感染的病例[14-15]。本研究中所有送检患者的G试验和GM试验均为阴性。G试验和GM试验对于诊断尖端赛多孢子菌肺炎的敏感性和特异性较低，不推荐将其作为诊断标准[6,12]。

二代测序技术（next-generation sequencing，NGS）是一种新兴的不依赖培养的微生物诊断方法，与传统培养相比，在病原体的分类和诊断方面具有较高的敏感性和特异性，特别是对于那些不常见或不可培养的病原体，同时具有检测时间短的优势。目前已有NGS协助诊断尖端赛多孢子菌感染的临床个案报告[16-17]，提示NGS可能是很有前景的早期诊断尖端赛多孢子菌感染的工具。本研究中8例患者由于经济原因未行NGS检测，故无法对该技术进行评估。

尖端赛多孢子菌引起局限性肺部感染的临床症状和影像学表现缺乏特异性，炎症标志物ESR和CRP仅轻度升高，G试验和GM试验阳性率低，使得早期诊断困难。治疗首选伏立康唑，患者总体预后良好。临床中应提高对该病特点的认识，以实现早期诊断和精准治疗。

作者贡献声明　张尧　病史收集，数据录入和分析，论文撰写。缪青，金文婷，马玉燕，王萌冉　病史收集，数据录入。胡必杰，潘珏　论文审校和修订。

利益冲突声明　所有作者均声明不存在利益冲突。

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(收稿日期:2021-07-10; 编辑:王蔚)

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(收稿日期:2022-02-21; 编辑:王蔚)